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The effectiveness of interpersonal psychotherapy for adolescents with depression

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Review: The effectiveness of interpersonal psychotherapy for adolescents with depression: a systematic review and meta-analysis

Running head: A Systematic Review and Meta-Analysis of the Efficacy of IPT-A for depression

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Background: Interpersonal psychotherapy for adolescents (IPT-A) is a manualised, time-limited intervention for young people with depression. This systematic review aimed to determine the effectiveness of IPT-A for treating adolescent depression. **Method:** A systematic search of relevant electronic databases and study reference lists was conducted. Any study investigating the effectiveness of IPT-A in 12-20 year olds with a depressive disorder was eligible. Synthesis was via narrative summary and meta-analysis. **Results:** Twenty studies were identified (10 randomised trials, 10 open trials/case studies), many of which had small sample sizes and were of varying quality. Following IPT-A, participants experienced large improvements in depression symptoms ($d=-1.48$, $p<0.0001$, $k=17$), interpersonal difficulties with a medium effect ($d=-0.68$, $p<0.001$, $k=8$) and in general functioning with a very large effect ($d=2.85$, $p<0.001$, $k=8$). When compared against control interventions, IPT-A was more effective than non-CBT active controls in reducing depression symptoms ($d=-0.64$, $p<0.001$, $k=5$), and was no different from CBT ($d=0.05$, $p=0.88$, $k=2$). There was no difference between IPT-A and active control interventions in reducing interpersonal difficulties ($d=-0.26$, $p=0.25$, $k=5$). **Conclusions:** IPT-A is an effective intervention for adolescent depression, improving a range of relevant outcomes. IPT-A is consistently superior to less structured interventions and performs similarly to CBT. However these conclusions are cautious, as they are based on a small number of controlled studies, with minor adaptions to the standard IPT-A protocol and/or were conducted by the intervention developers. Further robust RCTs are therefore required. The lack of superiority in IPT-A for improving interpersonal difficulties highlights a need for studies to explore the underpinning mechanisms of change.

Key Practitioner Message

- Interpersonal Psychotherapy for Adolescents (IPT-A) is an effective intervention for depression, demonstrating improvements in depression symptoms, interpersonal and general functioning.
- IPT-A appears superior to less structured active control interventions (such as clinical monitoring).
- Further high quality research is now required to provide more robust conclusions in relation to IPT-A's efficacy in comparison to other gold standard treatments for adolescent depression e.g. CBT.
- Research exploring the core mechanisms of change underpinning the effectiveness of IPT-A is needed.

Keywords: Interpersonal psychotherapy; IPT; depression; meta-analysis; adolescent; effectiveness

Introduction

Depression is ranked by the World Health Organisation as the single largest contributor to global disability with over 300 million people affected in 2017 (WHO, 2017). The lifetime prevalence of major depressive disorder is approximately 11% of adolescents, with around 7% experiencing the disorder within the past 12 months (Avenevoli, Swendsen, He, Burstein, & Merikangas, 2015; Klerman, Weissman, Rounsaville, & Chevron, 1984). The typical duration of a first episode of depression in adolescence is 1-2 years, and the majority go on to experience at least one further episode within 5 years (Dunn & Goodyer, 2006; Gledhill & Garralda, 2011). A substantial minority (around 20%) develop persistent depression into adulthood (Dunn & Goodyer, 2006), highlighting the need for effective psychological interventions targeting adolescents.

Interpersonal Psychotherapy (IPT) (Klerman & Weissman, 1993; Klerman et al., 1984) is a time limited, manualised psychotherapy, which was initially developed to treat major depression in adults. It focuses on the bi-directional link between interpersonal relationships and depression. The efficacy of IPT for depression has been demonstrated by a meta-analysis (Cuijpers et al., 2011) of 38 randomised controlled trials (RCTs) where, compared with standard care or waiting list controls, a moderate to large effect of IPT was found in adults and adolescents combined. Furthermore, combination treatment of IPT and pharmacotherapy was more effective in preventing relapse than pharmacotherapy alone, albeit there was some evidence that IPT may have less efficacy than pharmacotherapy independently. There was no evidence that IPT had greater efficacy than other psychotherapies, including cognitive behavioural therapy (CBT), although the number of comparison studies was too small to draw definitive conclusions.

IPT has since been adapted for use in a range of a clinical presentations including eating disorders (Fairburn et al., 1991; Wilfley et al., 1993), bipolar disorder (Frank, Kupfer, Ehlers, & Monk, 1994), post-traumatic stress disorder (Markowitz et al., 2015) and has been adapted for groups (Wilfley, Mackenzie, Welch, Ayres, & Weissman, 2000) and use with older adults (Hinrichsen & Clougherty, 2006). Adaptations have also been made for the younger age (under 12's) via Family Based IPT (Dietz, Mufson, Irvine, & Brent, 2008) and found to be more successful in achieving remission from depression than an individualised child-centred therapy (Dietz, Weinberg, Brent, & Mufson, 2015). A school based preventative group approach has also been developed: Interpersonal Psychotherapy-Adolescent Skills Training (IPT- AST) (Young, Mufson, & Schueler, 2016), for teenagers with sub-clinical symptoms of depression. Three RCTs (Horowitz, Garber, Ciesla, Young, & Mufson, 2007; Young, Mufson, & Davies, 2006; Young, Mufson, & Gallop, 2010) collectively indicate that

IPT-AST offers a promising new approach to preventing adolescent depression when delivered in a targeted manner.

Interpersonal Psychotherapy for adolescents (IPT-A) (Mufson, Dorta, Moreau, & Weissman, 2011) is a version of IPT designed for young people between 12-18 years with an acute onset depression. It is briefer than IPT (usually involving 12-16 sessions), involves a more developmentally appropriate approach to assessment, and includes parents and carers. Given these important differences from IPT, examining the efficacy of IPT-A is essential.

A network meta-analysis of psychotherapies for depression in children and adolescents based on RCTs only (Zhou et al., 2015) found that out of nine psychotherapies, only IPT and CBT were significantly more effective than control conditions post treatment. This was replicated at follow-up, although only IPT retained this superiority at both short and long term follow up. The authors acknowledged that this finding was based on a small number of trials and requires further validation. A key limitation of this review is that one-quarter of all the included IPT RCTs, and all IPT studies used to explore follow up, were based on the preventative IPT-AST model (Young et al., 2006; Young et al., 2010), which explicitly excludes young people who meet diagnostic threshold for depression. This limitation was replicated in a recent meta-analysis investigating the efficacy of IPT for adolescents (Pu et al., 2017) that concluded that IPT was significantly more effective than control conditions in reducing depressive symptoms at post treatment and follow up, and had superior acceptability, based on all cause discontinuation. However, the inclusion of preventative work and the exclusion of key RCTs comparing different formats of IPT-A (e.g., individual vs group IPT-A) (O'Shea, Spence, & Donovan, 2015; Rossello, Bernal, & Rivera-Medina, 2008) limits this review's capacity to draw clinically relevant conclusions for the treatment of adolescents with a diagnosis of depression. Finally, a recent review (Mychailyszyn & Elson, 2018) has focuses specifically on IPT-A but suffers from notable methodological problems including omission of key studies that would meet the review's inclusion criteria.

The current systematic review and meta-analysis aims to determine the effectiveness of IPT-A for adolescent depression. To draw on all available evidence of efficacy and effectiveness, the review will be inclusive of a range of methodological designs, including RCTs, non-randomised controlled trials and case series. Secondary aims include determining the impact of IPT-A on adolescents' interpersonal relationships, levels of functioning and treatment dropout.

Methods

Protocol and registration

The review protocol was prospectively registered in Prospero on 01/02/2016, registration number: CRD42016033888.

Eligibility criteria

Population. Studies were included if they examined the efficacy of IPT-A in adolescents, aged 12-20 years old, with a depressive disorder. Studies with samples of both adults and adolescents were eligible for inclusion if data on participants aged 12-20 years could be extracted separately or obtained from trial authors. Depression was defined as: major, minor or intermittent depression, or dysthymia as diagnosed according to standardised diagnostic criteria (including all variants of DSM and ICD); *or* depressive status, defined as scoring above cut-off on a standardised depression rating scale according to the original authors' definition. Studies where participants had comorbid secondary medical or other mental health conditions were not excluded; however, participants with a primary diagnosis of another major psychiatric disorder (e.g. schizophrenia, bipolar) were excluded.

Intervention and control conditions. All studies examining the impact of IPT-A via group or individual format were considered. Minor modifications to the original IPT-A protocol were accepted (e.g., population-based modifications, such as those for self-harming teenagers; and frequency or timing of sessions). Preventative depression interventions (e.g. IPT-AST) or IPT protocols targeting other presenting difficulties (e.g., binge eating) were excluded. Both controlled and uncontrolled studies were eligible for inclusion. For studies that used a control group, there were no restrictions on the format of the control.

Outcomes. For studies involving a control group, the primary outcome of efficacy was the mean difference in post intervention continuous depression severity scales between intervention and control groups. Post intervention was defined as assessments conducted immediately following the final session of the pre-specified acute phase of treatment. Any maintenance/booster sessions were not included as the acute phase of treatment. For studies without a control group, the primary outcome of efficacy was the mean change in continuous depression severity scales from baseline to post intervention. The secondary outcome of efficacy was the proportion of patients who responded to treatment, defined as substantial overall improvement from baseline as stated by the original investigators (e.g. more than a 50% reduction a continuous measure of depressive

symptoms). When 'response' was not reported, we used 'remission', if available. Remission was defined as a reduction in symptoms to within the normal range (e.g., using established scale cut-offs). For studies with a control group, we examined the difference in response/remission between control and intervention groups. The impact of IPT-A on functioning and interpersonal difficulties was assessed via the mean difference in post intervention scores of continuous scales between intervention and control groups, or via change from baseline to post intervention in non-controlled studies. For both outcomes we prioritised global measures (e.g., those that assessed general interpersonal difficulties rather than focusing on one specific relationship, such as conflict with a parent). After the acute phase treatment, we assessed follow up effects (maximum of 12 months) across all efficacy outcomes. If some participants took further treatments, including continued treatment, booster sessions or any other psychotherapies or antidepressants during the follow-up period, they were excluded from these analyses of follow up effects. Dropout, used as a proxy measure of acceptability of treatment, was determined by the proportion of participants who discontinued (all causes) treatment by post intervention. If this data was not available, data regarding drop out from assessments post intervention was used instead. Studies were excluded if they were written in a language other than English. In order to address publication bias, both published and unpublished studies were included and efforts were made to source unpublished studies.

Information sources

The following electronic databases were searched on the 17th November 2018: PsycINFO; Web of Science; Embase; MEDLINE; CINHAL Plus; and ASSIA. A comprehensive search of unpublished theses and dissertations via ProQuest Dissertation Abstracts and Opengrey was completed. Hand searches of reference lists of trials identified in the initial searches and relevant review papers were also conducted.

Search

Searches were conducted using the following keywords: Interperson* or Interpersonal Psychotherapy or IPT; and Depress*; and Adolescen* or Child* or Teen* (see Online Appendix S1 for a full search strategy).

Study selection

The results of searches were extracted and stored in Endnote. One reviewer (FD) screened the titles and abstracts of potential studies and articles that clearly did not meet the eligibility criteria were excluded. Two reviewers (FD and HS) then independently assessed the full texts of all remaining studies against eligibility criteria. There was 100% agreement between reviewers in this process. Reasons for exclusion were recorded.

Data collection process

The data extraction tool (available on request) was piloted on three studies initially and no amendments were made. In cases where multiple manuscripts were associated with a single study, data were extracted across manuscripts in chronological order starting with the primary publication and adding further information for additional manuscripts (e.g., follow up, secondary outcomes) where appropriate. Data extraction for each article was performed independently by two reviewers (FD and HS) and agreement in this process was excellent (absolute agreement = 98.6%, n=1134 items extracted in total). All discrepancies (n=22) were resolved mutually between the respective reviewers, with a third reviewer (MS) consulted if required.

Data items

The following data were extracted: study characteristics (first author, year of publication, geographical location, study design, length of follow up); population characteristics (sample size, age, gender, race/ethnicity, illness severity, comorbidities); experimental conditions (intervention conditions, control conditions, fidelity assessment); and outcomes in all arms (mean and standard deviation of continuous measures of depression severity at baseline, post intervention and follow up and correlation between time points; proportion of participants with substantial improvement in depression severity and/or reduction of symptoms to the 'normal' range at post-intervention and follow up; mean and standard deviation of continuous measures of functioning and interpersonal difficulties at baseline, post intervention and follow up and correlation between time points; proportion of patients who discontinued treatment by post intervention).

Risk of bias in individual studies

Risk of bias in RCTs was assessed using the Cochrane Risk of Bias Tool. As per the rest of data extraction, risk of bias was determined independently by two reviewers (FD and HS).

Summary measures

The summary measures for meta-analysis were standardised mean difference (for continuous outcomes between and within groups), and odds ratios (for binary outcomes). Where studies included multiple ratings of the same outcome we prioritised patient-reported outcomes over clinician-reported outcomes. If more than one self-report measure was used, primary outcome measures were prioritised. Where studies included multiple control groups, we prioritised comparisons against active control interventions (e.g. CBT, treatment as usual etc.) over comparisons against waiting list/no intervention.

Synthesis of results

Summary was via a combination of narrative synthesis and meta-analysis. Random effects meta-analyses were performed using the "metafor" package in R (Viechtbauer, 2010). The standardized mean difference for each condition was computed with $d = Mean_{diff}/SD_{diff}$, where $Mean_{diff}$ denotes the mean of the change scores, $SD_{diff} = \sqrt{(SD^2_{pre}+SD^2_{post} -2rSD_{pre}SD_{post})}$, and r denotes the correlation between the pre and post-intervention/ control assessments. If SD_{diff} was not reported, the paired-samples t-test value was employed to calculate the effect size with $d = t\sqrt{n}$. The sampling variance of the d-values was calculated with $v=1/n+d^2/2n$, where n denotes the group size. Correlations between the pre- and post-intervention/ control measurements were calculated for all studies that reported the necessary values. Of note, r can be inferred when only SD_{diff}, SD_{pre}, and SD_{post} are known. For studies where r was unknown and SD_{diff} had to be computed in order to obtain d, the mean correlation was employed to impute r. I^2 and the Q statistic were used to examine heterogeneity between estimates. Given the wide range of treatment and control conditions included in the review, effect modification by treatment (e.g. group vs. individual) and control condition type (CBT vs. non-CBT) was also explored by adding type of condition as a categorical moderator using a weighted least squares approach, reflecting the difference in effect size for the two levels of the moderator (Viechtbauer, 2010).

Risk of bias across studies

Publication bias (i.e., nonpublication of small trials with null results) was examined with the trim and fill method (Duval & Tweedie, 2000), using the "metafor" package in R (Viechtbauer, 2010).

Additional analyses

No additional analyses were planned.

Results

Electronic and hand searches revealed 9,356 studies to be screened for eligibility (Figure 1). The majority of these studies (n=9,257) were excluded by screening title and abstracts, leaving 99 studies to be examined at full text. This process resulted in 34 papers, describing 20 unique studies, being included in the review. Reasons for exclusion are shown in Figure 1.

[Insert Figure 1 about here]

Study characteristics

Of the 20 included studies, 10 were randomised controlled trials, 7 open clinical trials and 3 case studies (see Table 1). Studies were published between 1994 and 2018 with most conducted in the USA (n=14), two in Puerto Rico, and one in Australia, Uganda, Canada and Taiwan respectively. Sample sizes ranged from 1 to 314 per trial (median n=20), creating a total of 910 participants in the current review (IPT-A n=491, control n=419). Participants were between 12-20 years old and were predominantly female (68%). Six studies included a follow up ranging between 20 weeks and 52 weeks from intervention onset.

Interventions

Table 1 highlights the range of interventions examined. Ten studies used a standard individual IPT-A protocol over 12-16 weekly sessions, one of which included enhanced parental involvement (Gunlicks-Stoessel, Mufson, Cullen, & Klimes-Dougan, 2013). Three studies (Bolton et al., 2007; Miller, Gur, Shanok, & Weissman, 2008; Mufson, Gallagher, Dorta, & Young, 2004) assessed the efficacy of an IPT-A group, one of which (Miller et al., 2008) was an adaptation for pregnant teenagers. Two studies investigated individual IPT-A with adaptations for adolescents who self-harmed (Jacobson & Mufson, 2012; Tang, Jou, Ko, Huang, & Yen, 2009), one reported on a brief form of individual IPT-A (Mufson, Yanes-Lukin, & Anderson, 2015), one on a brief version adapted for pregnant adolescents (Bledsoe et al., 2018) and one study reported on a stepped care model of IPT-A (Mufson et al., 2018). Two studies directly compared group and individual formats of IPT-A (O'Shea et al., 2015; Rossello et al., 2008). Seven of the 20 included studies (Bolton et al., 2007; Mufson, Dorta, Wickramaratne, et al., 2004; Mufson et al., 2018; Mufson, Weissman, Moreau, & Garfinkel, 1999; Rossello & Bernal, 1999; Rossello et al., 2008; Tang et al., 2009) included a non IPT-A control group (3 of the RCTs compared different formats/intensities of IPT-A only), ranging from waiting list, clinical monitoring, treatment as usual, creative play and CBT.

[Insert Table 1 about here]

Outcomes

Two studies did not report continuous measures of depression at pre and post intervention (Mufson, Gallagher, et al., 2004; O'Hara, 2001). The eighteen remaining studies provided data on a range of self-report and clinician-rated measures (see Online Resources Table S1). Only two studies (Bolton et al., 2007; Santor & Kusumakar,

2001) reported response rates with nine reporting on remission (Bledsoe et al., 2018; Bolton et al., 2007; Miller et al., 2008; Mufson, Dorta, Wickramaratne, et al., 2004; Mufson et al., 1994; Mufson et al., 1999; O'Shea et al., 2015; Rossello et al., 2008; Santor & Kusumakar, 2001). The impact of IPT-A on interpersonal and general functioning was measured by nine and 11 studies respectively (see Online Resources Table S2). Finally, acceptability of treatment, as measured by the proportion of individuals who discontinued treatment, was calculated for 17 studies, with required data not being reported in three studies (Bolton et al., 2007; Miller et al., 2008; O'Shea et al., 2015).

Risk of bias within studies

The methodological quality of studies varied significantly (see Table 2 for individual risk of bias ratings) as a result of a high number of studies failing to fully report methodological protocols. From the ten RCTs included in the review, half reported using appropriate methods for randomisation, with the other half not providing enough detail to determine how the groups were randomised. Only two RCTs (20%) reported adequate concealment of allocation, with the majority of studies (80%) failing to report enough information to ascertain whether intervention allocations could have been foreseen prior to, or during enrolment. The risk of both detection and attrition biases was rated as low in the majority of RCTs (70%). The potential of bias from selective reporting was concerning with four studies rated as high risk (40%) and 6 studies (60%) not reporting enough information to rule out selective reporting, largely as a consequence of no study protocol being published. It should also be noted that 90% of RCTs were rated as "unclear" for other risk of bias, as a high number of studies were authored by the developers of IPT-A.

[Insert Table 2 about here]

Results of individual studies

Depression symptoms. A meta-analysis examining change in depression symptoms between pre and post intervention revealed a large significant improvement in depression symptoms following IPT-A (d=-1.48, 95% CI: -1.75; -1.21, p<0.0001, k=17; I^2=73.9%, Q(16)=49.88, p<0.001) (see Figure 2). When exploring treatment format, no significant interaction effect was found between group and individual IPT-A delivery on depression symptoms (Q(1) = 2.03, p=0.15; *b*=0.49, SE=0.34, *p*=0.15). Therefore, all other results will be presented with group and individual IPT-A delivery combined. A meta-analysis comparing baseline to follow up (ranging from 20 to 52 weeks) depression symptoms revealed a large significant effect showing improvement in depressive symptoms following IPT-A through to follow up (d=-1.12, 95% CI: -1.40; -0.84, p<0.0001, k=5; I^2=9.01%,

Q(4)=6.09, p=0.19). There was no effect modification by length of follow up (20-24 weeks vs 52 weeks) (Q(1) = 2.30, p = 0.13; b = -0.40, SE = 0.27, p = 0.13).

[Insert Figure 2 about here]

A meta-analysis comparing post intervention depression symptoms between IPT-A and active control interventions, revealed a small significant effect in favour of IPT-A (d=-0.41, 95% CI: -0.75;-0.07, p=0.02, k=7; I^2=73.3%, Q(6)=26.89, p<0.001). Given that this analysis included a range of active control interventions, including less structured interventions such as treatment as usual and clinical monitoring, we explored effect moderation by control type (CBT vs non-CBT intervention). There was a significant moderation effect by control type (Q(1)=8.38, p<0.01; *b*=0.74, SE=0.25, *p*<0.001): when compared against CBT there was no significant difference in post intervention depressive symptoms (d=0.05, 95% CI: -0.62; 0.73, p=0.88, k=2; I^2=71.9%, Q(1)=3.55, p=0.06); however, when compared against a non-CBT active control conditions there was a medium significant effect in favour of IPT-A (d=-0.64, 95% CI: -0.86; -0.43, p<0.0001, k=5; I^2=12.4%, Q(4)=4.51, p-0.34) (Figure 3). Only one study (Rossello & Bernal, 1999; RCT, n=48) compared IPT-A to an active control at follow up (24 weeks) and found no significant difference between IPT-A and CBT.

[Insert Figure 3 about here]

Treatment response and remission. Only two studies assessed treatment response. In an open trial (n= 25), Santor and Kusumakar (2001) found that 84% of participants achieved response using IPT-A. In contrast in an RCT (n=314) Bolton et al. (2007) found a 37% response in IPT-A, although this compared favourably to a 14% response in waiting list controls and a 13% response in those receiving creative play (X^2 (2) = 24.74, p<0.001). No studies assessed treatment response through to follow up.

Nine studies (4 open trials and 5 RCTs) explored remission rates in IPT-A, with estimates ranging from 29% (Bolton et al., 2007; RCT, n=105) to 100% (Mufson et al., 1994; open trial, n=14). Seven of those studies (4 open trials and 3 RCTs) had remission rates over 70% for at least one means of assessing remission. There were significantly higher remission rates in IPT-A compared with active controls (OR=2.46, 95% CI: 0.01; 5.92, p=0.05, k=4; I^2=70.6%, Q(3)=11.62, p<0.01), and significant moderation effect by control type, (Q(1)=10.37, p<0.01; *b*=1.58, SE=0.49, *p*<.01), with IPT-A demonstrating significantly higher remission rates when compared against non-CBT control conditions only (OR=3.97, 95% CI: 2.18; 7.17, p<0.001, k=3; I^2=0%, Q(3)=1.25, p=0.53). Two studies reported remission rates at follow up: Mufson et al. (1994; open trial, n=14)

reported 90% remission rate at 52 weeks, and O'Shea et al. (2015; RCT, n=39) reported 77% remission rate at 52 weeks. No studies reported remission rates at follow up in comparison to controls.

Interpersonal difficulties. There were significant reductions in interpersonal difficulties from pre intervention to post intervention in IPT-A with a medium effect (d=-0.68, 95% CI: -0.93; -0.43, p<0.001, k=8; I^2=61.3%%, Q(7)=18.17, p=0.01) (see Figure 4). However, there was no significant difference in interpersonal difficulties between IPT-A and active controls (d=-0.26 95% CI: -0.69; 0.18, p=0.25, k=5; I^2=71.4%, Q(4)=15.92, p=0.003) and no moderation by control type (Q(1)=0.25, p=0.61; *b*=0.24, SE=0.49, *p*=0.61). Two studies reported on changes in interpersonal difficulties from post-intervention to follow up within IPT-A (Mufson et al., 1994, open trial, n = 14; O'Shea et al., 2015, RCT, n=39), both showing maintenance of reduction in interpersonal difficulties through to 52 weeks. Only one study (Rossello & Bernal, 1999; RCT, n=48) compared interpersonal difficulties in IPT-A to an active control at follow up (24 weeks) and found no significant difference between IPT-A and CBT.

[Insert Figure 4 about here]

General functioning. A meta-analysis found significant improvements in general functioning from pre-intervention to post-intervention in IPT-A with a very large effect (d=2.85, 95% CI: 1.37; 4.34, p<0.001, k=8; I^2=96.1%, Q(7)=63.13, p<0.001) (see Figure 5). Only two studies compared general functioning between IPT-A and an active control condition (Mufson, Dorta, Olfson, Weissman, & Hoagwood, 2004; Mufson et al., 2018). These studies showed significantly better general functioning at post-intervention in those receiving IPT-A compared with control conditions, with a small effect (d= 0.44, 95% CI: 0.06; 0.82, p=0.02, k=2; I^2=0%, Q(1)=0.33, p=0.56) (see online resources Figure S1). Three studies reported general functioning at follow up. Miller et al. (2008; open trial, n=11) and O'Shea e al. (2015, RCT, n=39) report maintenance in improvements in functioning from post-intervention to 20 weeks and 52 weeks respectively, however Mufson et al. (1994; open trial, n=14) report a deterioration in functioning at 52 weeks back to pre-intervention levels. No studies compared general functioning in IPT-A to an active control at follow up.

[Insert Figure 5 about here]

Dropout. A meta-analysis showed no difference in all cause dropout in IPT compared with other active control conditions (OR=0.59, 95% CI: 0.31; 1.09, p=0.09, k=7; I^2=25.3%, Q(6)=8.61, p=0.20) (see online resources, Figure S2), and no effect modification by control type (Q(1)=2.22, p=0.13; *b*=1.09, SE=0.73, *p*=.14).

Risk of bias across studies. Implementation of the trim and fill approach resulted in minor amendments to estimated effect sizes for some outcomes, providing some evidence of publication bias in the results. However, these changes were consistently small and did not have any implications for the conclusions drawn, suggesting that the stated results are relatively robust. Adjusted estimates following trim and fill procedures are available for all outcomes upon request.

Discussion

This is the first meta-analysis assessing a range of clinical outcomes associated with IPT-A for adolescents meeting clinical threshold for depression. A strength of this meta-analysis is the investigation of clinically relevant research outcomes and as a result, it will be of significant interest to clinicians, health care providers and policy makers, alongside researchers. IPT-A has been shown to be an effective treatment for adolescent depression, demonstrating large significant improvements in depression symptoms post intervention, with some evidence that these are maintained for up to one year. No interaction was found between group and individual delivery of IPT-A, indicating that both modalities could be delivered to good effect. However, there are fewer trials investigating group IPT-A, therefore further exploration of this treatment format would be beneficial.

There was a small significant effect in favour of IPT-A improving depressive symptoms in comparison to other active treatments, with this effect being moderated by the type of intervention used as a control condition. When compared with CBT, a structured, evidence-based treatment for adolescent depression, there was no significant difference between the groups in post intervention depression symptoms. However, a medium significant effect was present when IPT-A was compared to other active, but less structured, interventions such as treatment as usual, clinical monitoring and play therapy. These findings were mirrored by remission rates with IPT-A demonstrating significantly higher remission rates from depression post intervention when compared to non-CBT control conditions. The results of this meta-analysis should increase clinicians' and healthcare providers' confidence that IPT-A serves as an effective treatment for adolescent depression, and can be offered as part of a range of evidence-based interventions, promoting service user choice and treatment options. However, it should be noted that these conclusions are based on a small number of controlled studies with varying risk of bias ratings. Moreover, some studies involved minor adaptations to the standard IPT-A protocol, and many have been conducted by the academic group involved in the development of the intervention. Many of the meta-analyses had high heterogeneity in intervention effects suggesting that there may

be further moderators of effectiveness that were not fully explored in the current review. There is now a need to prioritise robust RCT methodology to extend our understanding of the efficacy of IPT-A in comparison to other evidence based pharmacological and psychological treatments for adolescent depression.

IPT-A did produce a medium-sized significant reduction in interpersonal difficulties post intervention but there was no difference between IPT-A and active controls, regardless of modality. Taking into account IPT-A's dual clinical focus of improving interpersonal relationships and depression symptoms, this is a surprising result that warrants further investigation and highlights the need to explore the underpinning mechanisms associated with IPT-A. Despite an empirically grounded theoretical rationale and efficacy associated with this approach, little is known about precisely how and why IPT-A works. Innovative research methodology such as the Experience Sampling Method (ESM) could provide opportunities to investigate specific underpinning mechanisms of this therapy (Lemmens, Müller, Arntz, & Huibers, 2016). Furthermore, taking into account that there was no significant difference in post intervention depression symptoms between CBT and IPT, and the clinical similarities in some shared generic and specific therapeutic techniques (e.g. psycho-education, decision analysis, etc.), these methods could also play an important part in determining potential common factors underpinning these effective therapeutic approaches (Wampold, 2015). Of course, similarity in outcomes on average between samples does not rule out the differential effectiveness of interventions for individuals, and so these findings also support further work regarding moderators of treatment outcome so that interventions can be targeted at those for whom they will be most effective (Huibers et al., 2015).

This meta-analysis indicates that IPT-A is an effective intervention for adolescent depression. However, the evidence base includes a large number of small studies, uncontrolled trials and studies of varying quality. There is now a need to move beyond pre-post open trials of IPT-A and associated pilot adaptions to specialist groups, to robust RCTs and methodologies with significant clinical implications. Such trials are now taking place, for example, Gunlicks-Stoessel and colleagues (Gunlicks-Stoessel, Mufson, Westervelt, Almirall, & Murphy, 2016) conducted a feasibility SMART [Sequential Multiple Assignment Randomized Trial (Lavori & Dawson, 2000, 2003)] to begin to explore adaptive treatment strategies, mirroring stepped care protocols for IPT-A (e.g. extending treatment protocols and supplementing with anti-depressant medication, determined by participants early response to IPT-A). A pilot trial of feasibility and acceptability of a brief model of IPT-A covering 6 sessions within primary care (Mufson et al., 2015) mirrors this exploration of ideal treatment length

and the potential to adapt protocols based on clinical need. Both of these studies are pilot trials with further exploration of efficacy required.

Limitations

There were some limitations associated with the studies included in the review with a high number failing to fully report methodological protocols specifically around random allocation, associated concealment and information related to blinding of assessors. These risk of biases, alongside the potential of selective reporting, could be remedied in the future by studies pre-registering trial protocols. Furthermore, the developers of IPT-A authored a high number of studies highlighting an ongoing need for external academic groups to begin to replicate and extend findings.

The meta-analysis also suffered from some limitations. First, the trials reviewed were small and of varying quality and evidence from open trials and case reports is also subject to bias. Overall, there was a lack of studies with long term follow up, in particular those comparing maintenance to other active therapies, meaning robust conclusions on longer term maintenance cannot be drawn. While it was positive that IPT-A outcomes could be compared to those of CBT, there was a lack of trials exploring IPT-A in relation to other evidence based psychological therapies for adolescent depression (e.g., family therapy). Moreover, the limited number of trials comparing IPT-A to other psychological therapies precluded examination of predictors or moderators of treatment efficacy. Future work identifying characteristics associated with better outcomes in specific treatments would be valuable. Finally, the use of dropout is a coarse measure of acceptability of treatment, lacking clarity of underpinning reasons for exiting treatment early (including early recovery). In depth process evaluations would provide rich exploration of patients' experiences in IPT-A and provide context for drop out in particular subpopulations.

Conclusions

In conclusion, IPT-A is an effective intervention for adolescent depression, which improves depressive symptoms, interpersonal functioning and general functioning. The growing evidence base cautiously shows that IPT-A is superior to less structured active control interventions for adolescent depression (such as clinical monitoring), and has the potential to perform similarly to another gold-standard intervention, CBT. However, there is now a need to extend the evidence base using high quality RCTs as these conclusions are based on small

trials of varying quality, and many of the included trials have made minor adaptions to the standard IPT-A protocol and/or have been conducted by the developer of the intervention. Furthermore, despite the underpinning theoretical model in IPT-A targeting interpersonal functioning, it was surprising that IPT-A did not improve interpersonal functioning to a greater extent than any other active intervention. This finding highlights the need to further explore core mechanisms of change in established psychotherapies, including accounting for common factors that explain similarities across modalities.

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Ethical information

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Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of this article.

Appendix S1. Search strategy.

Table S1. Outcomes for depression symptoms, response and remission rates in included studies.

Table S2. Outcomes for interpersonal difficulties and general functioning in included studies.

Figure S1. Forest plot showing results of meta-analysis of standardised mean difference (SMD) in general functioning between IPT-A and control conditions.

Figure S2. Forest plot showing results of meta-analysis of odds ratios (OR) in dropout between IPT-A and control conditions.

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Figure Captions

Figure 1: PRISMA flow diagram of studies included in the review

Figure 2: Forest plot showing results of meta-analysis of standardised mean change (SMC) in depressive symptoms between pre and post IPT-A.

Figure 3: Forest plot showing results of meta-analysis of standardised mean difference (SMD) in depressive symptoms IPT-A and control conditions, by control type (top panel CBT control conditions, bottom panel other active control conditions).

Figure 4: Forest plot showing results of meta-analysis of standardised mean change (SMC) in interpersonal difficulties between pre and post IPT-A.

Figure 5: Forest plot showing results of meta-analysis of standardised mean change (SMC) in general functioning between pre and post IPT-A.

Table 1.

Study Characteristics

Study ID	Associated references	Design	N by arm	Format, # sessions	Follow up length	Country or region	Mean Age (SD) and Gender (% female)
Hall 09	(Hall & Mufson, 2009)	Case Study	IPT-A: 1	Individual, 12 sessions +1 booster	NA	USA	15.0 (NA) 0% f
Jacobson 12	(Jacobson & Mufson, 2012)	Case Study	IPT-ASI: 1	Individual, 12 sessions	24 wks	USA	18.0 (NA) 100% f
O'Hara 01	(O'Hara, 2001)	Case Study	IPT-A: 1	Individual, 12 sessions	N/A	USA	14 (N/A) 0% f
Bledsoe 18*	(Bledsoe et al., 2018)	Open Trial	IPT-BPA: 14	Individual, 8 sessions + 1 engagement	NA	USA	16.9 (1.7) 100% f
Miller 08*	(Miller et al., 2008)	Open Trial	IPT-PG: 11	Group, 12 sessions	20 wks	USA	16.5 (1.2) 100% f
Mufson 04a	(Mufson, Gallagher, et al., 2004)	Open Trial	IPT-A: 6	Group, 12 sessions + 4 individual	N/A	USA	NR 100% f

Mufson 15*	(Mufson et al., 2015)	Open Trial	IPT-A Brief: 10	Individual, 6 sessions	N/A	USA	15.3 (1.9) 80% f
Mufson 94*	(Mufson & Fairbanks, 1996; Mufson et al., 1994)	Open Trial	IPT-A: 14	Individual, 12 sessions	52 wks	USA	14.8 (NR) 86% f
Pasquinelli 09*	(Pasquinelli, 2009)	Open Trial	IPT-A: 4	Individual, 12 sessions	24 wks	USA	NR 75% f
Santor 01*	(Santor & Kusumakar, 2001)	Open Trial	IPT-A: 25	Individual, 12 sessions	N/A	Canada	16.2 (1.4) 92% f
Bolton 07*	(Betancourt et al., 2012; Bolton et al., 2007; Stein, 2010; Verdeli et al., 2008)	RCT	IPT-A: 105 Creative play**: 105 WL: 104	Group, 16 sessions	NA	Uganda	15.0 (1.1) 57% f
Gunlicks-Stoessel 13*	(Gunlicks-Stoessel & Mufson, 2016; Gunlicks-Stoessel et al., 2013)	RCT	IPT-A: 6 IPT-AP: 9	Individual, 12 sessions	NA	USA	15.2 (NR) 87% f
Gunlicks-Stoessel 16*	(Gunlicks-Stoessel et al., 2016; Gunlicks-Stoessel, Westervelt, Reigstad, Mufson, & Lee, 2017)	RCT	IPT-A: 40 (6 arms with supplemental sessions and/or medication)	Individual, 12-16 sessions	NA	USA	14.8 (1.8) 78% f

Mufson 04b*	(Gunlicks-Stoessel & Mufson, 2011; Gunlicks-Stoessel, Mufson, Jekal, & Turner, 2010; McGlinchey, Reyes‐Portillo, Turner, & Mufson, 2017; Mufson, Dorta, Wickramaratne, et al., 2004; Mufson, Yanes-Lukin, Gunlicks-Stoessel, & Wickramaratne, 2014; Reyes-Portillo, McGlinchey, Yanes-Lukin, Turner, & Mufson, 2017)	RCT	IPT-A: 34 TAU**: 29	Individual, 12 sessions	N/A	USA	15.1 (1.9) 54% f
Mufson 18*	(Mufson et al., 2018)	RCT	IPT-A: 29 (stepped care, 2 arms, supplemental sessions and medication) TAU**: 19	Individual, arm 1: 11 sessions, arm 3: 16 sessions	N/A	USA	15.9 (2.2) 79% f
Mufson 99*	(Mufson et al., 1999)	RCT	IPT-A: 24 Clinical Monitoring**: 24	Individual, 12 sessions	N/A	USA	15.8 (1.6) 73% f

O'Shea 15*	(O'Shea et al., 2015)	RCT	IPT-A Individual: 19 IPT-A Group: 20	Individual, 12 session + 4 booster sessions. Group, 10 sessions + 4 booster sessions	52 wks	Australia	15.3 (1.4) 85% f
Rossello 08*	(Rossello et al., 2008; Rossello, Bernal, & Rivera-Medina, 2012)	RCT	IPT-A Individual: 31 IPT-A Group: 29 CBT Individual**: 23 CBT Group**: 29	Individual and Group, 12 sessions	N/A	Puerto Rico	14.5 (1.9) 55% f
Rossello 99*	(Rossello & Bernal, 1999)	RCT	IPT-A: 23 CBT**: 25 WL: 23	Individual, 12 sessions	24 wks	Puerto Rico	14.7 (1.4) 54% f
Tang 09*	(Tang et al., 2009)	RCT	IPT-A: 35 TAU**: 38	Individual, 12 sessions	N/A	Taiwan	15.2 (1.7) 66% f

Note: IPT-A: Interpersonal Psychotherapy for Adolescents; IPT-BPA brief and adapted for pregnant adolescents; IPT-AP: IPT with enhanced involvement with parents; IPT-ASI: IPT with adaptation for self injury; IPT-PG: group IPT-A for depression in pregnant adolescents; NR: Not reported; NA: Not applicable; RCT: Randomised controlled trial; TAU: Treatment As Usual; WL: Wait List. *Included in meta-analyses. **Defined as active controls

Table 2.

Risk of bias within RCTs

Study	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other risk of bias
Bolton 07	Low	Low	High	Low	Low	High	Unclear
Gunlicks-Stoessel 13	Unclear	Unclear	High	Low	Low	High	Unclear
Gunlicks-Stoessel 16	Unclear	Unclear	High	Low	High	High	Unclear
Mufson 99	Low	Unclear	High	Low	Low	Unclear	Unclear
Mufson 04b	Low	Unclear	High	Low	Low	Unclear	Unclear
Mufson 18	Low	Unclear	High	Low	Low	Unclear	Unclear
O'Shea 15	Unclear	Unclear	High	Low	Low	Unclear	Low
Rossello 99	Unclear	Unclear	High	Unclear	Unclear	Unclear	Unclear
Rossello 08	Low	Low	High	Unclear	Low	High	Unclear
Tang 09	Unclear	Unclear	High	Unclear	Unclear	Unclear	Unclear